



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :  C07D 405/06		A1	(11) International Publication Number: WO 00/49014  (43) International Publication Date: 24 August 2000 (24.08.00)		
(21) International Application Number: PCT/GB00/00481		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).			
(22) International Filing Date: 15 February 2000 (15.02.00)					
(30) Priority Data: 9903472.0 17 February 1999 (17.02.99) GB					
(71) Applicants ( <i>for all designated States except US</i> ): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). SHIONOGI & CO. LTD. [JP/JP]; 1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541-0045 (JP).					
(72) Inventors; and		Published <i>With international search report.</i>			
(75) Inventors/Applicants ( <i>for US only</i> ): KOIKE, Haruo [JP/JP]; 1-3 Kuise Terajima 2-Chome, Amagasaki-shi, Hyogo 660-0813 (JP). KABAKI, Mikio [JP/JP]; 1-3 Kuise Terajima 2-Chome, Amagasaki-shi, Hyogo 660-0813 (JP). TAYLOR, Nigel, Philip [GB/GB]; Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). DIORAZIO, Louis, Joseph [GB/GB]; Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).					
(74) Agent: BRYANT, Tracey; Global Intellectual Property, Patents., AstraZeneca UK Limited, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).					
(54) Title: PROCESS FOR THE PRODUCTION OF TERT-BUTYL (E)-(6-[2- [4-(4-FLUOROPHENYL) -6-ISOPROPYL-2-[METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN-5-YL] VINYL](4R, 6S)-2,2-DIMETHYL [1,3]DIOXAN-4-YL) ACETATE					
(57) Abstract					
<p>The invention concerns a process for the manufacture of tert-butyl (E)-(6-[2- 4-(4-fluorophenyl) -6-isopropyl-2-[methyl (methylsulfonyl) amino] pyrimidin-5-yl] vinyl)-(4R, 6S)-2,2-dimethyl [1,3-dioxan-4-yl] acetate, the novel starting material used in said process and the use of the process in the manufacture of a pharmaceutical.</p>					

# BEST AVAILABLE COPY

BEST AVAILABLE COPY

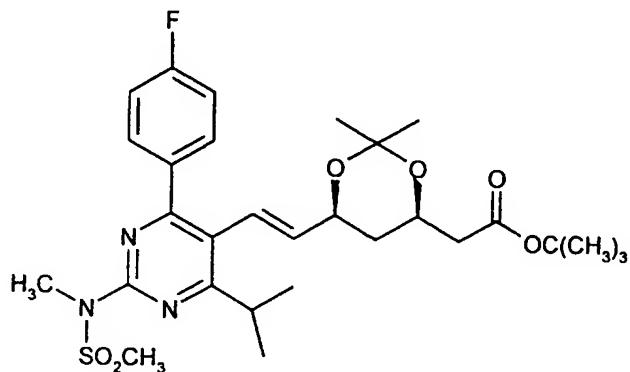
## FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CI	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

**PROCESS FOR THE PRODUCTION OF TERT-BUTYL (E)-(6-[2-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL]VINYL](4R,6S)-2,2-DIMETHYL[1,3]DIOXAN-4-YL)ACETATE**

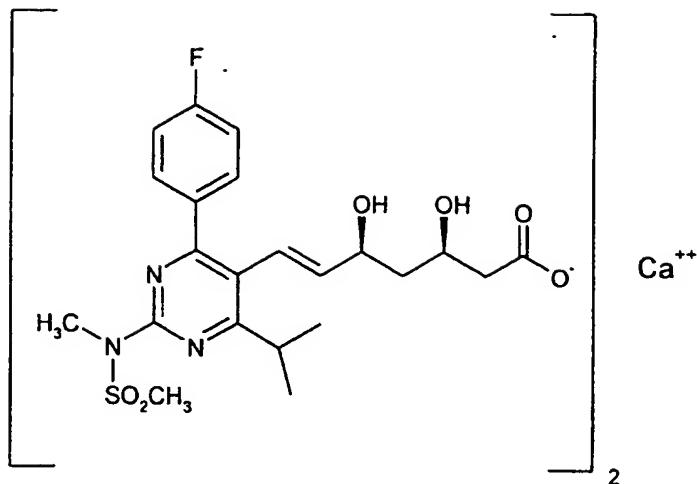
This invention concerns a novel chemical process, and more particularly it concerns a novel chemical process for the manufacture of tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate of formula I,



Formula I

10 (hereinafter referred to as BEM) which is useful, for example, as a chemical intermediate in the production of a pharmaceutical useful in the treatment of, *inter alia*, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis. The invention further includes the novel starting material used in said process and the use of the process in the manufacture of an HMG CoA reductase inhibitor.

15 In European Patent Application, Publication No. (EPA) 0521471 is disclosed (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid and its sodium salt and calcium salt (illustrated below)

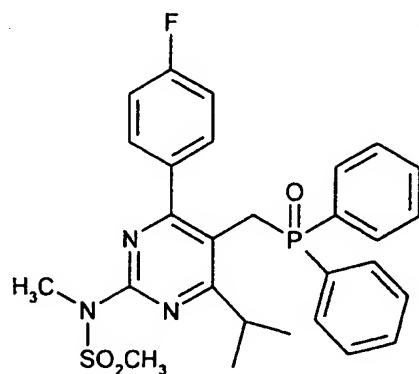


(hereinafter referred to collectively as "The Agent") as inhibitors of HMG CoA reductase.

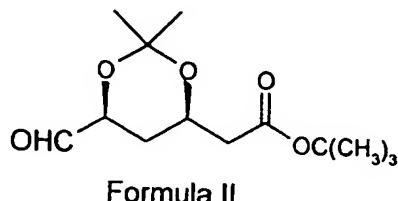
The Agent is obtained therein via reduction of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-

5 (N-methyl-N-methylsulfonyl-amino)pyrimidin-5-yl-(3R)-3-hydroxy-5-oxo-(E)-heptenoate and subsequent processing. However the Agent may be obtained from BEM by treatment with acid (to cleave the acetonide protecting group) followed by base (to cleave the ester) and (as described in EPA 0521471) conversion of the initially formed salt to the free acid or the calcium salt.

- 10 We have now discovered a useful and advantageous process for preparing BEM. According to the invention there is provided a process for preparing BEM (formula I) which comprises reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl] phosphine oxide of formula III



(hereinafter referred to as DPPO) with tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl}acetate of formula II



5

(hereinafter referred to as BFA) in the presence of a strong base.

The process is carried out in a suitable solvent, or mixture of solvents for example, ethereal or aromatic solvents or mixtures thereof. Particularly suitable solvents include, for example, tetrahydrofuran (THF), dimethoxyethane and toluene, or mixtures thereof.

10 Particularly preferred solvents include, for example, THF and THF and toluene.

Suitable bases for use in the process include, for example, amide bases, alkyl metals and metal hydrides. Particular bases include, for example, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide, butyllithium and sodium hydride. A particularly preferred base is, for example, sodium bis(trimethylsilyl)amide

15 (NaHMDS).

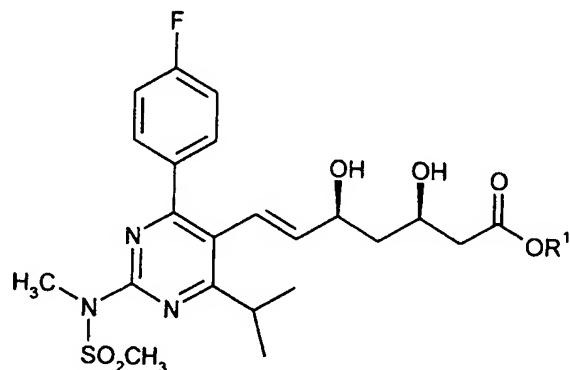
The reaction may be carried out at a temperature in the range of, for example, -20°C to -90°C, such as -40°C to -90°C, for example -40°C to -80°C. A convenient temperature at which to carry out the reaction is, for example, that of a mixture of acetone and solid carbon dioxide (about -75°C).

20 The process is advantageously carried out with 1.0 to 1.2 equivalents of base (per equivalent of DPPO), such as 1.05 to 1.2 equivalents and preferably 1.05 to 1.12 equivalents. Although BFA can be present in large excess, it is convenient to use 1.0 to 1.35 equivalents (per equivalent of DPPO), and preferably 1.05 to 1.3 equivalents, especially 1.05 to 1.15 equivalents.

25 The process of the invention provides significantly improved yields and quality of product by comparison to when a corresponding dialkyl phosphonate (-PO(Oalkyl)<sub>2</sub>) starting material is used instead of DPPO.

The starting material, DPPO, which is a further aspect of the present invention, may be obtained as described in the Examples hereinafter, starting from an alkyl 2-amino-4-(4-fluorophenyl)-6-isopropylpyrimidin-5-carboxylate, for example the methyl ester which may be obtained as described in Japanese Patent Application No. 06-256318, or the ethyl ester 5 which may be obtained as described in EPA 0521471. BFA may be obtained as described in EPA 0319847 (Example 6).

A further aspect of the present invention is a process for the manufacture of a compound of the formula IV



10

Formula IV

in which R<sup>1</sup> is hydrogen or a pharmaceutically acceptable cation, which comprises;

- (1) reaction of DPPO with BFA in the presence of a strong base (as described above) to give BEM;
- 15 (2) cleavage of the dihydroxy (acetonide) protecting group (for example by acid hydrolysis, such as by using HCl in THF or acetonitrile); and
- (3) cleavage of the *tert*-butyl ester group under basic conditions to form a compound of the formula IV in which R<sup>1</sup> is a pharmaceutically acceptable cation (for example by using a solution of a metallic hydroxide in a polar solvent, such as using aqueous sodium hydroxide 20 in ethanol or acetonitrile to form the sodium salt);
- optionally followed by neutralisation to give a compound of the formula IV in which R<sup>1</sup> is hydrogen;
- and/or optionally followed by conversion to another compound of the formula IV in which R<sup>1</sup> is a pharmaceutically acceptable cation (for example conversion of the sodium salt to the

# BEST AVAILABLE COPY

WO 00/49014

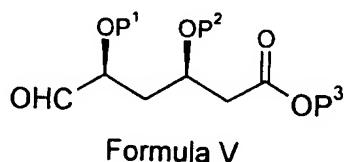
- 5 -

PCT/GB00/00481

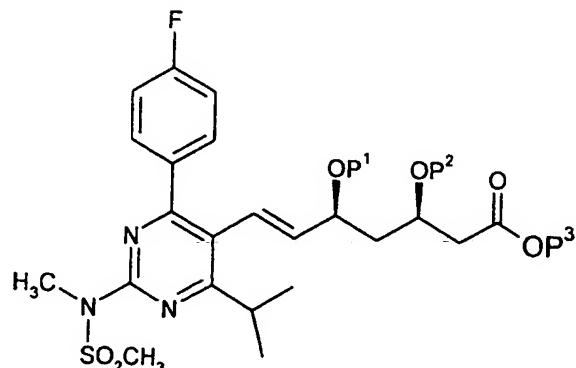
calcium salt by treatment with a water soluble calcium salt (such as calcium chloride) under aqueous conditions).

Suitable conditions for steps (2), (3) and the subsequent optional steps are analogous to, or the same as, those disclosed in EPA 0521471 and/or EPA 0319847, which are hereby 5 incorporated herein by reference. To obtain the calcium salt of the compound of formula IV, as illustrated on page 1, preferably steps (2), (3) and conversion to the calcium salt via the methylamine salt are carried out as described in Example 7, which steps form a further aspect of the invention.

It will be appreciated that, in the processes described above, BFA may be replaced by 10 a compound of the general formula V



in which P<sup>1</sup> and P<sup>2</sup> are alcohol protecting groups, or P<sup>1</sup> and P<sup>2</sup> taken together is a 1,3-diol 15 protecting group, such as those described in EPA 0319847 and GB 2244705 which are included herein by reference, and P<sup>3</sup> is a carboxylic acid protecting group, for example (1- 8C)alkyl (such as (1-4C)alkyl), to form a compound of the formula VI



The compound of the formula VI may be converted to the Agent by cleavage of the alcohol or 20 diol protecting groups and conversion of the COOP<sup>3</sup> to a COOH group or a pharmaceutically acceptable salt thereof. Such general processes form further features of the present invention.

The invention is further illustrated, but not limited by the following Examples.

Preparation 1Preparation of DPPO

A stirred mixture of methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate (12.0 g) in toluene (55ml) was 5 cooled to -10°C and diisobutyl aluminium hydride (50 ml of a 1.5M solution in toluene) was added over two hours maintaining the temperature below 0°C. After addition, the mixture was stirred for 30 minutes at 0°C. Methanol (0.64 ml) was added to the mixture maintaining the temperature at 0°C. The mixture was then added over two hours to a stirred mixture of concentrated hydrochloric acid (23.3 ml), water (40.5 ml) and acetonitrile (24 ml) at 40°C, 10 maintaining the temperature of the mixture at 40°C. After addition, the mixture was stirred at 40°C for a further 30 minutes and then purged with nitrogen (to remove any isobutane). The mixture was cooled to 20°C and allowed to stand for 20 minutes. The organic phase was separated and washed with a mixture of concentrated hydrochloric acid (0.7 ml) and water (30 ml). Acetonitrile (24 ml) was added to the organic phase and the mixture washed with a 15 solution of sodium bicarbonate (0.038 g) in water (120 ml).

The organic phase was heated to 40°C, and then from 40°C to 80°C using a nitrogen purge. The mixture was concentrated by distillation at atmospheric pressure, collecting 54 ml of distillate. Acetonitrile (24 ml) was added to the concentrated solution and phosphorus tribromide (1.2 ml) was added with stirring, maintaining the temperature of the mixture at 20 20°C. After addition, the mixture was stirred at 20°C for 30 minutes. The mixture was added to water (36 ml) over 30 minutes maintaining the temperature at 20°C. The mixture was stirred for 5 minutes and the organic phase separated. The organic phase was washed with a solution of sodium bicarbonate (0.027 g) in water (36 ml), followed by water (36 ml). The organic phase was distilled under reduced pressure until 29 ml of distillates was collected. 25 The mixture was cooled to 60°C and ethyl diphenylphosphinite (7.47 ml) was added. The mixture was stirred at 60°C for 3 hours, then heated to reflux. Toluene (40 ml) was added and the mixture cooled to 0°C over 2 hours. The product was collected by filtration, washed with cold toluene (10 ml) and dried under vacuum at 50°C to give DPPO (14.66 g); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 270 MHz): 7.42 [m, 10H, P(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>], 7.12 [m, 2H, Ar-H], 6.92 [m, 2H, Ar-H], 3.92 30 [d, 2H, CH<sub>2</sub>P], 3.51, 3.46 (2 x s, 6H, NCH<sub>2</sub>, SO<sub>2</sub>CH<sub>3</sub>], 3.43 [hept., 1H, CH(CH<sub>3</sub>)<sub>2</sub>], 1.25 [d, 6H, CH(CH<sub>3</sub>)<sub>2</sub>]

Methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate was prepared as follows:

A mixture of methyl 2-amino-4-(4-fluorophenyl)-6-isopropyl-pyrimidine-5-carboxylate (19.0 g), sodium tert-pentoxide (22.95 g) and dimethoxyethane (190 ml) was stirred for 30 minutes at 25°C. The stirred mixture was cooled to -10°C and methanesulfonyl chloride (8.4 ml) was added dropwise, maintaining the temperature of the mixture at -5°C. After 20 minutes, dimethyl sulfate (8.1 ml) was added and the mixture allowed to warm to 25°C. The mixture was stirred for one hour at 25°C and a solution of sodium tert-pentoxide (1.91 g) in dimethoxyethane (10 ml) added. The mixture was stirred for one hour at 25°C. A solution of sodium chloride (13.3 g) in water (133 ml) was added and the mixture was stirred for 10 minutes at 25°C. The mixture was allowed to settle for 15 minutes and the lower aqueous phase was separated and discarded. Water (38 ml) was added to the remaining mixture and the mixture was stirred for 30 minutes at 25°C. The mixture was then heated to obtain a complete solution. The mixture was cooled slowly to 25°C over one hour. The mixture was cooled to 0°C, stirred for one hour, and the suspended solid collected by filtration. The solid was washed with cold (0°C) solution of 50:50 water/dimethoxyethane (20 ml). The solid was dried under vacuum at 60°C to give methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate (19.35 g); <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 7.69 (m, 2H), 7.14 (m, 2H), 3.71, 3.60, 3.51 (3 x s, 9H), 3.20 (m, 1H), 1.32 (d, 6H).

#### Example 1

A mixture of DPPO (19.17 g) and THF (227 ml) were warmed briefly to 40°C until a clear solution had formed then inerted by the sequential application of vacuum and nitrogen (5 cycles). The mixture was immersed in an acetone/CO<sub>2</sub> bath cooling the contents to -75°C. Sodium bis(trimethylsilyl)amide (37.4 ml of 1.0M solution in THF) was added to the reaction mixture over 10 minutes from a pressure equalising dropping funnel maintaining the temperature below -74°C and forming a red solution of the anion. THF (10 ml) was rinsed through the dropping funnel into the mixture and the mixture stirred a further 1 hour at -76°C forming a red suspension. BFA (80 ml of ~13.5% w/w toluene solution) was added in portions to the suspension over 20 minutes from a pressure equalising dropping funnel maintaining the temperature below -73°C. Toluene (20 ml) was rinsed through the dropping

funnel into the mixture and the mixture stirred a further 15 minutes at -76°C. The chilling bath was lowered and the suspension allowed to warm to 10°C over 1.5 hours. Glacial acetic acid (3.21 g) in water (15 g) was added in one portion raising the temperature to 18°C and dissolving all solids and the mixture was stirred a further 5 minutes.

- 5       The mixture was concentrated by distillation at atmospheric pressure (jacket 110°C) to a temperature of 94°C collecting a total of 274 ml distillates. The concentrated mixture was cooled to 40°C, water (40 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded. Sodium hydrogen carbonate (2.99 g) in water (40 ml) was added and the mixture stirred for 5 minutes then allowed to  
10 settle for 15 minutes. The lower aqueous phase was discarded. Water (30 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded.

The organic phase was transferred to a distillation apparatus with toluene (20 ml) and concentrated by distillation at atmospheric pressure (jacket 125-130°C) to a temperature of  
15 116°C collecting 85 ml distillates. Vacuum was applied (400-500 mbar) and a further 16.5 ml distillates collected to a temperature of 111°C. The vacuum was released and the concentrated mixture allowed to cool to 80°C. Warm MeOH (140 ml, 50°C) was added with rapid stirring and the batch allowed to self-cool to 20°C over 30 minutes during which time a solid was deposited. The suspension was further cooled to 2°C for 30 minutes then the solid  
20 was collected by filtration on a sinter and pulled as dry as possible. The solid was washed with cold MeOH (60 ml, 2°C) and again pulled as dry as possible then transferred to a vacuum oven and dried overnight (50°C, 200 mbar); giving BEM (14.01 g, 67.7%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)

7.65 [m, 2H, Ar-H], 7.09 [m, 2H, Ar-H], 6.52 [dd, 1H, ArCH=CH], 5.47 [dd, 1H,  
25 ArCH=CH], 3.57, 3.50 [2 x s, 6H, NCH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>], 3.38 [hept., 1H, Ar-CHMe<sub>2</sub>], 2.45, 2.30 [2 x dd, 2H, CH<sub>2</sub>CO<sub>2</sub>tBu], 1.55, 1.13 [dt, dd, 2H, acetonide CH<sub>2</sub>], 1.50, 1.40 [2 x s, 6H, acetonide C(CH<sub>3</sub>)<sub>2</sub>], 1.45 [s, 9H, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>], 1.27 [dd, 6H, ArCH(CH<sub>3</sub>)<sub>2</sub>]

Examples 2-6

- 30       The procedure as described in Example 1 was carried out using the ratios of reactants and the temperatures given in Table 1. There was thus obtained BEM in the yields given.

**Table 1**

Wt DPPO	Temp. (°C)	Eq. NaHMDS	Eq. BFA	BEM Yield
10.00 g	-75	1.12	1.20	69.2%
18.12 g	-75	1.12	1.20	69.6%
12.08 g	-75	1.06	1.26	72.8%
19.17 g	-40	1.05	1.06	56.7%
9.57 g	-90	1.05	1.10	72.0%
9.57 g	-60	1.05	1.10	70.1%

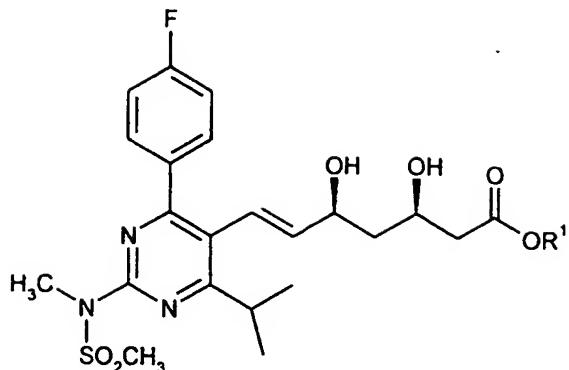
**Example 7**

5 A mixture of BEM (5.0 g) and acetonitrile (35 ml) was stirred under an inert atmosphere at 40°C. 0.02M hydrochloric acid (9.5 ml) was added over 30 minutes to the resultant solution, maintaining the temperature at 35°C to 42°C. The mixture was stirred at 40°C for 3 hours then cooled to 25°C. 1.0M sodium hydroxide solution (9.5 ml) was added with stirring at 25°C and the mixture was stirred for an additional one hour at 25°C. Sodium 10 chloride (4.7 g) was added and the mixture was cooled to -5°C over one hour. Sufficient of a solution of 1M hydrochloric acid (9.5 ml) and sodium chloride (2.4 g) was added at -5°C to achieve a pH of 3.4 to 4.0 and the mixture stirred at this temperature for 5 minutes. The mixture was allowed to settle for 10 minutes at -5°C to give two layers. The lower layer was separated and discarded. Acetonitrile (65 ml) at -5°C was added to the remaining solution and 15 the mixture was filtered through a filter agent. 40% methylamine solution in water (1.1 ml) was added at -5°C and the mixture was warmed to 30°C over 40 minutes and maintained at this temperature for 90 minutes. The mixture was then cooled to 0°C over 40 minutes and maintained at this temperature for 90 minutes. The resultant solid was collected by filtration and washed with acetonitrile (2x12 ml). The solid, which is the methylamine salt of the 20 compound of formula IV ( $R^1 = MeNH_3^+$ ), was dried under vacuum at 35°C (3.87 g). 8% w/w aqueous sodium hydroxide (5.44 ml) was added to a stirred mixture of the methylamine salt (6.0 g) in degassed water (30 ml) at 20°C and the mixture was stirred for one hour. The mixture was filtered and concentrated under reduced pressure at 40°C until 24 ml of distillate collected. Water (24 ml) was added and the mixture again concentrated under reduced

pressure at 40°C until 24 ml of distillate collected. Water (30 ml) was added and a solution of calcium chloride dihydrate (1.03 g) in water (6 ml) was added dropwise at 20°C. The mixture was stirred for 45 minutes and the resultant solid filtered. The solid was washed with water (36 ml) and dried under vacuum at 40°C to give the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid.

Claims

1. A process for the manufacture of tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}-(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate which comprises reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the presence of a strong base.
2. A process as claimed in claim 1 wherein the reaction is carried out at a temperature in  
10 the range of -20°C to -90°C.
3. A process as claimed in claim 1 or 2 wherein the strong base is sodium bis(trimethylsilyl)amide.
- 15 4. A process as claimed in claim 1, 2 or 3 wherein the reaction is carried out in a solvent selected from tetrahydrofuran, dimethoxyethane and toluene, and mixtures thereof.
5. A process as claimed in any of claims 1 to 4 wherein 1.0 to 1.2 equivalents of base are used per equivalent of the phosphine oxide.  
20
6. A process as claimed in any of claims 1 to 5 wherein 1.0 to 1.35 equivalents of tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate are used per equivalent of the phosphine oxide.
- 25 7. The compound diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide.
8. The compound tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}-(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate.  
30
9. A process for the manufacture of a compound of the formula IV



in which R<sup>1</sup> is hydrogen or a pharmaceutically acceptable cation which comprises

5 (1) reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the presence of a strong base to give tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate of formula I;

10

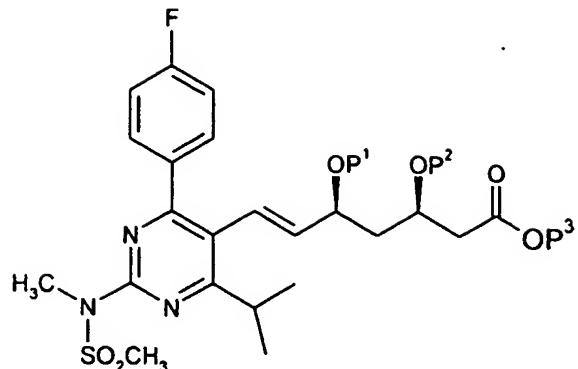
(2) cleavage of the dihydroxy protecting group from the product of step (1);

(3) cleavage of the tert-butyl ester group under basic conditions from the product of step (2) to form a compound of the formula IV in which R<sup>1</sup> is a pharmaceutically acceptable cation;

15

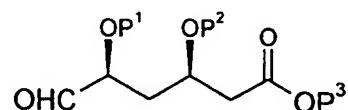
optionally followed by neutralisation to give a compound of the formula IV in which R<sup>1</sup> is hydrogen; and/or optionally followed by conversion to another compound of the formula IV in which R<sup>1</sup> is a pharmaceutically acceptable cation.

20 10. A process for the manufacture of a compound of the formula VI



Formula VI

which comprises reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with a compound of  
5 the formula V



Formula V

in the presence of a strong base, wherein P<sup>1</sup> and P<sup>2</sup> are alcohol protecting groups, or P<sup>1</sup> and P<sup>2</sup> taken together is a 1,3-diol protecting group, and P<sup>3</sup> is a carboxylic acid protecting group.

# BEST AVAILABLE COPY

## INTERNATIONAL SEARCH REPORT

Intn. 1st Application No  
PCT/GB 00/00481

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D405/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	G. WEISS ET AL.: "Stereoselective synthesis of HR 780, a new highly potent HMG-CoA reductase inhibitor" TETRAHEDRON LETTERS, vol. 31, no. 18, 1990, pages 2545-2548, XP002010060 * Scheme 2 *	1-10
Y	T. MINAMI, T. HIYAMA: "A novel enantioselective synthesis of HMG Co-A reductase inhibitor NK-104 and a related compound" TETRAHEDRON LETTERS, vol. 33, no. 49, 1992, pages 7525-7526, XP000886341 * Scheme 1 *	1-10 -/-
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the International filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the International filing date but later than the priority date claimed		
Date of the actual completion of the International search  <b>27 April 2000</b>		Date of mailing of the International search report  <b>17/05/2000</b>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <b>Herz, C</b>

## BEST AVAILABLE COPY

## INTERNATIONAL SEARCH REPORT

Inten	ned Application No
PCT/GB 00/00481	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	T. MINAMI ET AL.: "Stereoselective reduction of beta, delta-diketo esters derived from tartaric acid. A facile route to optically active 6-oxo-3,5-syn-isopropylidenedioxyhexanoate, a versatile synthetic intermediate of artificial HMG Co-A reductase inhibitors" TETRAHEDRON LETTERS, vol. 34, no. 3, 1993, pages 513-516, XP000886348 page 516	1-10
Y	T. HIYAMA ET AL.: "Synthesis of Artificial HMG-CoA Reductase Inhibitors Based on the Olefination Strategy" BULL. CHEM. SOC. JPN., vol. 68, no. 1, 1995, pages 364-372, XP000886402 * Scheme 3 * table 1	1-10
Y	WO 97 19917 A (L'OREAL) 5 June 1997 (1997-06-05) claim 47	1-10

**BEST AVAILABLE COPY**  
**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Internat'l Application No  
PCT/GB 00/00481

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719917 A	05-06-1997	FR 2741620 A EP 0805800 A JP 10504845 T	30-05-1997 12-11-1997 12-05-1998